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ATTENUATION OF CARDIOVASCULAR RESPONSE TO INTUBATION WITH LIDOCAINE 1.5 mg/kg VERSUS LABETALOL 10 mg

A thesis submitted in partial fulfillment of the
requirements for the degree of
Master of Science in Nurse Anesthesia
at Virginia Commonwealth University

BY

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The University of Utah, 1980

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Richmond, Virginia
July, 1990

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This is to certify that the thesis prepared by Randy LeRoy McGee entitled **ATTENUATION OF CARDIOVASCULAR RESPONSE TO INTUBATION WITH LIDOCAINE 1.5 mg/kg Versus LABETALOL 10 mg** has been approved by his committee as satisfactory completion of the thesis requirement for the degree of Master of Science in Nurse Anesthesia.

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LIST OF ABBREVIATIONS

Ach.....acetylcholine

ANS.....autonomic nervous system

ASA.....American Society of Anesthesiologists

BP.....blood pressure

dTc.....d-Tubocuarine

HR.....heart rate

IV.....intravenous

kg.....kilograms

Min.....minute

mg.....milligrams

mg/kg.....milligrams per kilogram

mm Hg.....millimeters of mercury

PNS.....parasympathetic nervous system

Sch.....succinylcholine

Sec.....seconds

SNS.....sympathetic nervous system

Abstract

ATTENUATION OF CARDIOVASCULAR RESPONSE WITH LIDOCAINE 1.5 mg/kg AND LABETALOL 10 mg

Randy L. McGee, BA, BSN

School of Allied Health Professions -- Virginia Commonwealth University, 1990.

Major Director: James P. Embrey, MSNA, CRNA

The purpose of this double blind study was to determine if labetalol 10 mg or lidocaine 1.5 mg/kg would blunt the cardiovascular responses to laryngoscopy and oral endotracheal intubation compared to a control. Thirty subjects undergoing surgical procedures were randomly assigned and evenly distributed to one of three groups. The labetalol 10 mg group, lidocaine 1.5 mg/kg group or normal saline (control) group. All subjects were classified ASA I or II. The preoperative medication, induction were standardized for all subjects with the exception of study medications. The labetalol subjects received 10 mg IV 5 minutes prior to laryngoscopy. The lidocaine subjects received 1.5 mg/kg 60 seconds prior to laryngoscopy. The control group received normal saline. All medications were given in a double blind fashion. The parameters recorded were heart rate, systolic and diastolic blood pressure and cardiac rhythm at 1 minute intervals throughout the study.

Analysis of covariance (ANCOVA) was used to determine whether the difference within groups and between groups were significant. A .05 level of significance was selected prior to commencement of the study. It was found that there was no significant differences between groups in blunting the cardiovascular responses to endotracheal intubation. Both lidocaine and labetalol had a significant effect on controlling a rise in heart rate and systolic blood pressure. However neither lidocaine or labetalol had any significant effect on preventing a rise in diastolic blood pressure. Therefore cardiovascular responses to oral endotracheal intubation were not attenuated by the administration of either lidocaine 1.5 mg/kg or labetalol 10 mg.

Chapter One

Introduction

A primary goal in the administration of general anesthesia is the maintenance of normal cardiovascular dynamics. With the development of the endotracheal breathing tube, a plethora of pharmacological agents and combination of agents have been used to attenuate the cardiovascular responses to the stress of endotracheal tube placement.

Preliminary studies of the circulatory effects of anesthesia in treated and untreated hypertensive subjects demonstrate that most subjects experience three periods of circulatory instability during induction, tracheal intubation, and emergence from general anesthesia and extubation. Hypertension, tachycardia and arrhythmias are common and well documented occurrences associated with laryngoscopy and tracheal intubation (Barash, Cullen & Stoelting, 1989).

Increases in blood pressure and pulse are accompanied by corresponding elevations of circulating levels of the catecholamines epinephrine and norepinephrine.These

transient elevations evoked by laryngoscopy and endotracheal intubation are probably not deleterious to the healthy subject. Increases in both heart rate and blood pressure may jeopardize tissue viability in subjects with valvular heart disease, coronary artery disease or elevations in intracranial pressure (Derbyshire et al., 1983). Dingle (1966) and Forbes and Dalley (1970) suggests that the hypertensive response of normotensive individuals to laryngoscopy and intubation may be enhanced and prove to be deleterious to hypertensive individuals.

The advantages of endotracheal intubation are many (a) patency of the airway is well ensured, (b) anatomic dead space is reduced, (c) control of subject's respirations are facilitated, and (d) access to tracheobronchial tree for suctioning of secretions is improved. Positive pressure can be used without fear of abdominal distention. The subject may be placed in any position without fear of comprising the airway if endotracheal intubation is maintained. The anesthetist may distance himself from the subject if needed for surgical access and still maintain control of respirations (Miller, 1986).

Induction of anesthesia using intravenous agents became popular in the 1950's (King, Harris, Griefenstein, Edder & Dripps, 1951). This type of induction replaced inhalation techniques. The intravenous induction offered the benefits of a shorter induction time, facilitating ease of

intubation, and promoting assurance of airway protection. However, the anesthetist had to accept the cardiovascular responses associated with laryngoscopy and oral endotracheal intubation produced in this light plane of anesthesia.

Various pharmacologic drug combinations have been used to partially suppress the cardiovascular response to endotracheal intubation. These drug combinations include intravenous lidocaine, selective and nonselective beta-blockers, selective and nonselective alpha-blockers, vasodilators, narcotics and non-narcotic pain relievers (Miller, 1986).

It was the purpose of this study to evaluate cardiovascular stability during induction and endotracheal intubation comparing lidocaine 1.5 mg/kg, labetalol 10 mg and a placebo when given intravenously prior to laryngoscopy. If either drug proved to provide cardiovascular stability during the stimulation, then that method could be used to decrease the stress response to laryngoscopy and endotracheal intubation. Increased knowledge from research in this area benefit subjects in terms of safety, comfort, cost and convenience.

Statement of Purpose

The purpose of this study was to determine the difference in the ability of either labetalol 10 mg IV 5 minutes prior to intubation, or Lidocaine 1.5 mg/kg 60

seconds prior to intubation to attenuate the cardiovascular responses to oral endotracheal intubation.

Statement of Problem

Is there a difference in the degree of attenuating the cardiovascular responses to oral endotracheal intubation in subjects pretreated with either labetalol 10 mg or lidocaine 1.5 mg/kg?

Hypothesis

There is no difference in the cardiovascular responses to direct laryngeal visualization and oral endotracheal intubation in subjects receiving either lidocaine 1.5 mg/kg or labetalol 10 mg or a placebo intravenously.

Variables

Independent variables. Independent variables were lidocaine 1.5 mg/kg and labetalol 10 mg.

Dependent variables. Dependent variables were the cardiovascular responses which include heart rate, blood pressure, and rhythm.

Definition of terms

Arrhythmia. Irregular heart action caused by disturbances, either physiological or pathological, in discharge of cardiac impulses from SA node and their

transmission through conductive tissue of the heart, as displayed on a standard EKG monitor.

ASA classification. The ASA classification is a definition of physical status adopted by the American Society of Anesthesiologists. Classifications pertaining to this study are defined as follows:

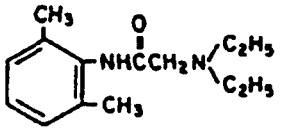
ASA I- Healthy Subject

ASA II- Subject with mild systemic disease without functional limitations.

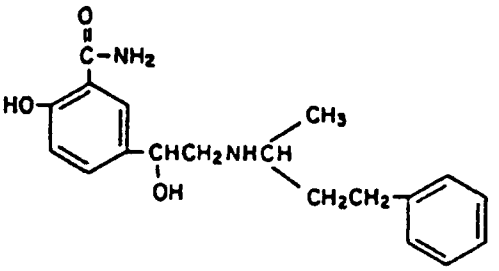
Cardiovascular response. The hypertension and tachycardia that occur in response to laryngoscopy and intubation.

Hypertension. Hypertension was defined as a systolic blood pressure greater than 140 mm Hg and a diastolic blood pressure greater than 90 mm Hg.

Labetalol. Labetalol is an antihypertensive agent that possesses both nonselective beta-adrenergic blocking as well as selective alpha-blocking properties (see Figure 1). Labetalol lowers blood pressure by decreasing the peripheral vascular resistance through alpha-blockade. Tachycardia is reduced by nonselective beta blocking properties of labetalol. The ratios of alpha- to beta-blockade is 1:7 after IV administration. The full antihypertensive effect of a single IV dose of labetalol (less than 1 mg/kg) is evident within 5 minutes of administration (Inada, 1989).



Lidocaine



Labetalol.

Figure 1. Chemical structure for labetalol and lidocaine. Note. From Pharmacology and Physiology in Anesthesia Practice (pp. 149, 203) by R. K. Stoelting, 1989, Philadelphia: Lippincott

Laryngoscopy. Laryngoscopy is the technique by which the larynx and glottis are directly visualized using a laryngoscope (see Figure 2).

Lidocaine. Lidocaine is an amide local anesthetic introduced by Lofgren in 1943. It has been shown to produce intense analgesia at near toxic levels (5 ug/ml). Low dose

IV Lidocaine has been demonstrated to decrease opioid requirements for post operative pain, and also has been shown to reduce anesthetic requirements for inhalation agents. It is believed that lidocaine reduces cerebral blood flow by increasing cerebral vascular resistance resulting in central nervous system depression (Stoelting, 1977).

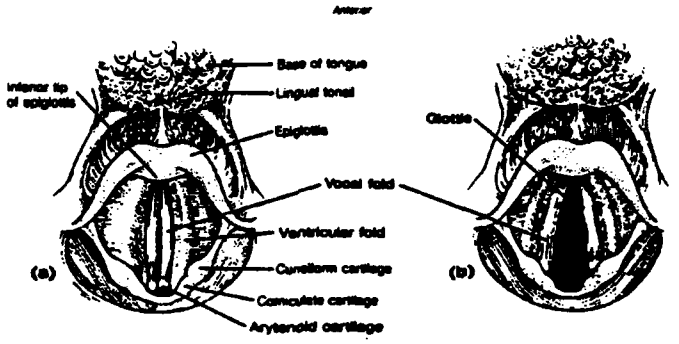


Figure 2. Glottis as viewed during laryngoscopy.
Note. From Basics of Anesthesia (p. 166) by R. K. Stoelting and R. D. Miller, 1989, New York: Churchill Livingstone

Oral endotracheal intubation. Process by which the true vocal cords are viewed with the aide of a laryngoscope for the insertion of an endotracheal tube into the trachea through the glottis for the entrance of oxygen (see Figure 2).

Tachycardia. Tachycardia is defined as a heart rate greater than 100 beats per minute or a heart rate greater than 30 percent above the base line measurement.

Assumptions

1. Increases in blood pressure and heart rate during induction are related to catecholamine release and not from other physiologic causes.

2. Blood pressure and heart rate that remain within the subject's normal limits during laryngoscopy indicate adequate blunting of the cardiovascular response to intubation.

3. The equipment used to measure the hemodynamic functions of the heart for this study are accurate in the measurement of the cardiovascular parameters.

Limitations

1. This study uses a small sample which limits generalizations of findings beyond the group studied.

2. Changes in heart rate and blood pressure may occur from other causes in addition to an inadequate amount of drug.

3. Individual subjects respond differently to preoperative medications and pharmacological agents.

4. The level of stimulation produced by different anesthetists performing laryngoscopy may lead to

fluctuations in the cardiovascular responses to laryngoscopy and intubation.

Delimitations

1. The study was conducted in a major, mid-Atlantic, university medical center.

2. Only individuals who were ASA I or II without history of congestive heart failure, unstable angina, bronchospastic disease or bronchodilator use, atrioventricular block, severe hepatic dysfunction, or current use of alpha- or beta- adrenergic drug administration were included in the study.

3. Subjects who were pregnant or breast feeding were also excluded from the study.

Conceptual Framework

Cardiovascular response to laryngoscopy. The placement of an endotracheal tube in the trachea is an extremely noxious stimulus. In response to this stimulation, there is a significant rise in catecholamine levels. This results in a rise in heart rate, systolic blood pressure, diastolic blood pressure and potential for cardiac arrhythmias. These responses to endotracheal tube placement are known as the cardiovascular response to endotracheal intubation (Wycoff, 1960). To develop a more thorough understanding of how to control the cardiovascular responses to oral endotracheal

intubation a basic understanding of the autonomic nervous system and the anatomy of the larynx is necessary.

Autonomic nervous system. The efferent portion of the nervous system that controls the visceral functions of the body is called the "autonomic nervous system" (ANS). By definition the term "autonomic nervous system" implies self-control and independence of outside influences, thus this term may be somewhat misleading. The autonomic nervous system has also been referred to as the involuntary or vegetative system. Although, conscious control of its activity is not possible, the ANS is influenced by centers located in the central nervous system. The limbic system can transmit signals to the lower centers and in this way influence autonomic control, these efferent impulses are actually set off by afferent impulses that travel to the central nervous system from the viscera and other autonomically innervated structures such as the larynx.

The main nerve centers for these Autonomic reflex arcs are located in the spinal cord, brain stem, and hypothalamus. Nerve impulses that arise in peripheral structures are transmitted to these centers by afferent fibers. The integrating centers at various levels of the CNS then respond by sending out efferent impulses via the ANS pathways. These then adjust the functioning of the various visceral organs in ways that keep the body's internal environment constant (homeostasis). The ANS regulates blood

pressure, heart rate, body temperature, and water balance among other things. This moment to moment control is exerted by a never ending interplay through two major subdivisions called the sympathetic (SNS) and parasympathetic nervous systems (PNS) (see Figure 3). The PNS sets the predominant autonomic tone of the body in the adult. It is concerned with homeostasis. The SNS sets the predominant autonomic tone of the body in the child. In both the adult and the child, the SNS predominates when the body is stressed and functions to return the body to homeostasis. The SNS and PNS usually function as physiologic antagonists such that activity of organs innervated by both divisions of the ANS represents a balance of each component's influence. In general, the PNS is concerned with conservation and restoration of physiologic parameters, while the SNS division governs processes involving an expenditure of energy. Most areas of the body demonstrate dual nervous innervation of both the PNS and SNS. Body function is a ratio between the two systems such that one system is never totally dominant over the other (Guyton, 1986).

Parasympathetic nervous system. The nerves of the PNS leave the central nervous system through cranial nerves III, V, VII, IX, and X and from the sacral portions of the spinal cord (Guyton, 1986). The X cranial or vagus nerve supplies PNS innervation to the heart, lungs, esophagus, stomach,

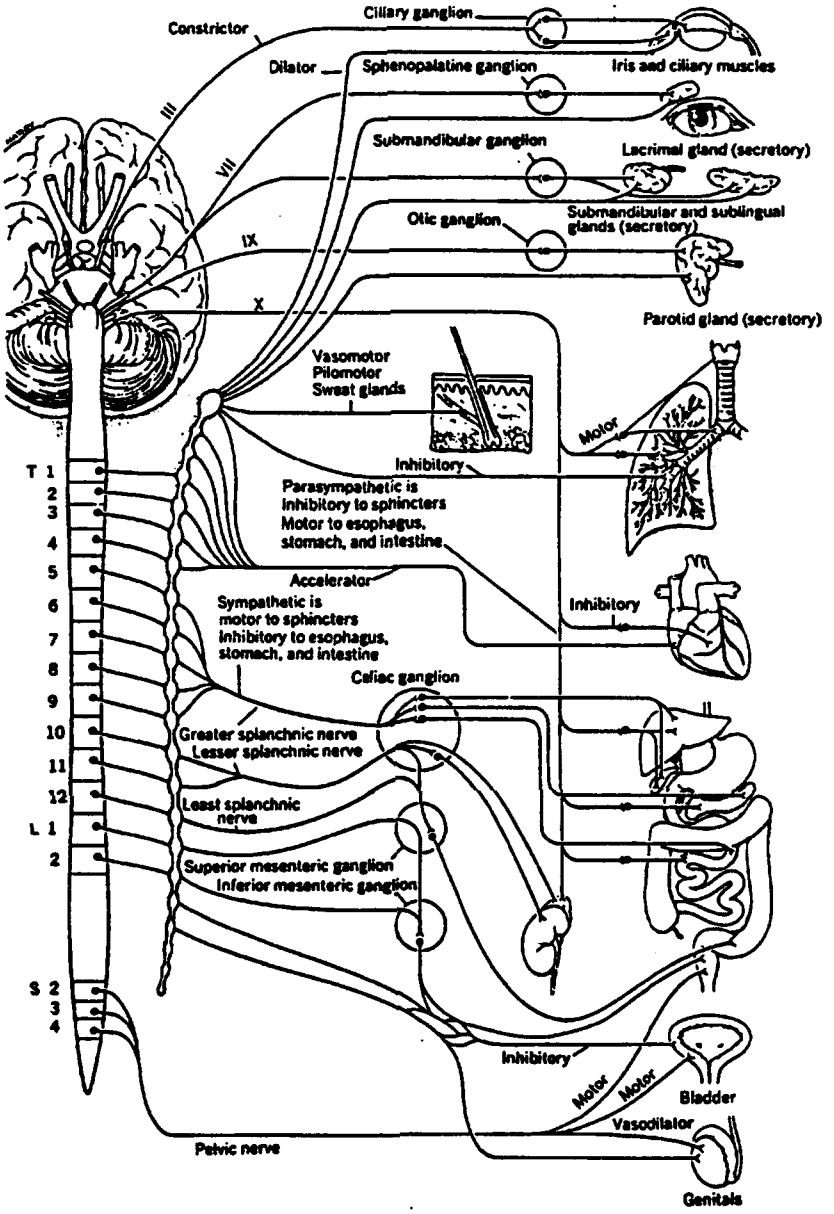


Figure 3. The autonomic nervous system.

Note. From Pharmacology and Drug Therapy in Nursing (2nd ed.) (p. 318) by J. M. Rodman and D. W. Smith, 1979, Philidelphia: New York.

small intestine, proximal portion of the large intestine, liver, gall bladder, pancreas, and upper portions of the ureters. Cranial nerve III passes to the eye, cranial nerve VII innervates the lacrimal, nasal, and submaxillary glands; cranial nerve IX innervates the parotid glands and portions of the neck. The fibers of the PNS pass uninterrupted to the innervated organs where they synapse with a short post synaptic neuron at or near the target organ. Acetylcholine (Ach) is the neurotransmitter secreted at the axon terminal in the effector organ (Guyton, 1986). Therefore all of these fibers are said to be cholinergic because they secrete Ach at their nerve endings.

Sympathetic Nervous System. The SNS is active at all times. Whenever any part of the SNS is stimulated, the entire system is stimulated. It is stimulated by stress including surgical stimulation and laryngoscopy. Nerves from the SNS arise from the thoracolumbar (T1 to L2) segments of the spinal cord (Guyton, 1986). These nerve fibers pass to the paravertebral sympathetic chains located lateral to the spinal cord. Cell bodies of preganglionic neurons are in the intermediolateral horn of the spinal cord. There are 22 pairs of Ganglia comprising the paravertebral sympathetic chain. In the paravertebral sympathetic chain, the preganglionic fibers synapse with the postganglionic fibers which pass upwards or downwards in the chain. The postganglionic fibers exit the paravertebral

ganglia traveling to the various peripheral target organs. A few of the postganglionic endings of the sympathetic nervous system, like the PNS, secrete acetylcholine and are cholinergic in nature. The vast majority of SNS postganglionic nerve endings secrete norepinephrine. These fibers are said to be adrenergic, a term derived from noradrenalin which is a common English term for norepinephrine. Thus, there is a basic functional difference between the respective postganglionic neurons of the PNS and SNS, one secreting Ach and the other secreting principally norepinephrine.

Neurotransmitters. Norepinephrine and acetylcholine act as neurotransmitters which interact with receptors in cell membranes. This proposed interaction activates the enzyme adenylate cyclase which results in the formation of cyclic AMP or it may alter permeability of cell membranes to various ions (Stoelting, 1987).

The existence of multiple receptors for adrenergic agonists and antagonists was first suggested by Dale in 1906. He demonstrated that some of the effects of epinephrine could be antagonized by ergot alkaloids, while other responses were not affected. Ahlguist in 1948 studied the effects of catecholamine which led to the development of the concept of alpha and beta-adrenergic receptors.

Subdividing these receptors into $alpha_1$ (postsynaptic) and $alpha_2$ (presynaptic), $beta_1$ (cardiac), and $beta_2$ (non cardiac) allows us to better understand how drugs act as either an agonist or antagonist at these various sites (Miller, 1986). Presynaptic $alpha_2$ receptors function as a negative feed back loop. Their activation inhibits subsequent release of norepinephrine. The differentiation of alpha receptors was first described by Langer in 1981. The concept of an $alpha_1$ and an $alpha_2$ adrenergic receptor is based upon selectivity of the receptors for receptor specific ligands (Exton, 1985). The target tissue response to a given dose of drug differentiates $alpha_1$ and $alpha_2$ receptors. Norepinephrine is known to stimulate both receptors; however, norepinephrine is a stronger agonist at $alpha_1$ sites (Exton, 1985). Clonidine is a relatively "selective" agonist for $alpha_2$ sites (Langer, 1981).

$Alpha_1$ receptors are located in vascular smooth muscle, intestinal mucosa, and splanchnic beds (Osswald et al., 1983). Activation of these receptors results in increased or decreased tone depending upon the target organ. Alpha receptors are presynaptic and postsynaptic. Stimulation of presynaptic $alpha_2$ receptors mediates inhibition of norepinephrine release (Langer, 1981). Norepinephrine causes vasoconstriction through $alpha_1$ stimulation while also inhibiting its own release via the negative feedback mechanism of the $alpha_2$ receptor (Fuder, 1985).

Postsynaptic alpha$_2$ receptors, like alpha$_1$ receptors, cause vasoconstriction. The difference between the two postsynaptic receptors is based upon affinities for various alpha agonists (Exton, 1985). Stimulation of presynaptic alpha$_2$ receptors may also involve stimulation of postsynaptic alpha$_2$ receptors resulting in a negation of it's effect (Exton, 1985). While each of these receptors has multiple functions, the vascular functions are as follows:

1. Activation of alpha$_1$ receptors causes vasoconstriction.

2. Activation of alpha$_2$ receptors results in decreased release of norepinephrine and decreased sympathetic tone via a central negative feedback mechanism.

Beta-adrenergic receptors. Beta receptors are the best understood of the SNS receptors; the key substance involved in the mediation of responses elicited by activation of beta-adrenergic receptors is cyclic AMP (see Figure 4). Norepinephrine is hypothesized to interact with the enzyme adenylate cyclase in the cell membrane (Miller, 1986).

The catecholamine-binding portion of the beta-adrenergic receptor is oriented in such a way that the poorly lipid soluble norepinephrine does not transverse the lipid barrier to activate the receptor. Activation is carried out by a series of messengers. The first messenger,

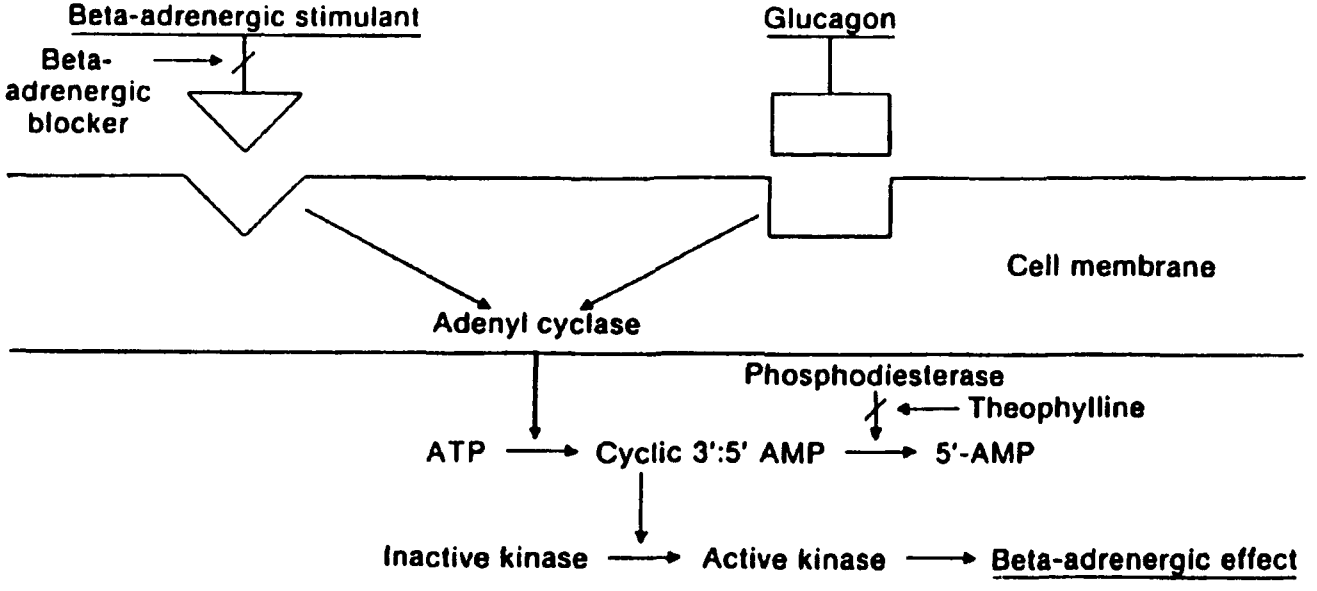


Figure 4. Schematic diagram of a proposed model for the Beta receptor

Note. From Cardiac Anesthesia (Vol. 2) (p. 183) by J. A. Kaplan, 1983, Orlando: Grune & Stratton.

adenylate cyclase, catalyzes the conversion of ATP to the second messenger cyclic AMP. Which then initiates a series of intracellular events resulting in the metabolic and physiologic effects considered typical of beta-adrenergic receptor stimulation by norepinephrine or agonist drugs (Miller, 1985).

Like the alpha receptors, actions of the catecholamines, norepinephrine and epinephrine, can be classified by the type and subtype of receptor where they exert their effect. While each of these receptors has various functions, the cardiac and vascular functions are as follows:

1. Activation of $beta_1$ receptors causes an increase in myocardial contractility, conduction velocity, and automaticity.

2. Activation of $beta_2$ receptors causes vasodilatation, bronchodilatation, and tachycardia.

Control of blood pressure. Normal control of blood pressure is accomplished by the proper functioning of three negative feedback systems. One of these mechanisms controls cardiac function (heart rate and stroke volume), another controls vascular tone (dilation and constriction), and a third influences blood volume (renal mechanisms). This third mechanism is a relatively long process involving days and weeks. The first two mechanisms are neural processes

which occur rapidly to control cardiovascular function (West, 1985).

Cardiovascular control is modulated through a baroreceptor feedback system. The baroreceptors consist of stretch receptors located within the carotid sinus and aortic arch. The afferent impulses are transmitted, respectively, over Cranial Nerve (CN) IX and CN X to the nucleus tractus solitarii (NTS) in the medulla. These impulses are then coordinated to other areas including the cardioinhibitory center. From the NTS, inhibitory neurons project to the vasomotor center in the ventrolateral medulla. Impulses generated in the baroreceptor inhibit the tonic discharge of the vasoconstrictor nerves and excite the cardioinhibitory center. Thus, the result is vasodilation, a decrease in blood pressure, bradycardia, and a decrease in cardiac output (West, 1985).

Within the normal range of blood pressure, the fibers of the aortic arch and carotid sinus discharge at a slow rate. When the pressure rises, the discharge rates increase; when the pressure falls, the discharge rate decreases. When pressures exceed 170 mm Hg, changes in blood pressure no longer result in nerve activity changes meaning the system has no further effect on blood pressure. It is important to remember that changes in efferent sympathetic and parasympathetic activity induced by the baroreceptor system have a variety of effects on the heart

and circulation. For example, decreases in carotid sinus pressure increase sympathetic tone, and produce increase cardiac contractility, decrease venous capacity, and therefore an increase in blood pressure. Conversely, increases in blood pressure result in decreases in sympathetic outflow and increases in parasympathetic outflow to the heart and vasculature. This causes a decrease in contractility, a decrease in stroke work, an increase in stroke volume and a decrease in heart rate, as well as the previously mentioned vasodilation (Berne & Levy, 1988).

Loss of baroreceptor function results in arterial pressure lability. Studies of sino-aortic deafferentation describe the regulatory role of these mechanisms. However, it has become increasingly evident that the baroreceptors do not influence lability (Jacob, Barres, Machaclo & Brody, 1988). The interaction between neural, humoral, and local tissue factors suggest that disruption of the integrity of the whole system results in lability. Jacob et al. (1988) reports on several studies investigating possibilities of pressure lability . The researchers conclude that combined ganglionic and alpha adrenergic blockade reduce lability, but not to pretreatment control levels. This indicates that the sympathetic nervous system plays a major role, but is not the only mechanism involved, in pressure lability. Arterial pressure lability is not simply loss of baroreceptor function or central mechanisms. It is the

interaction between neural and humoral components that determines lability. Jacob et al. (1988) conclude:

> Our preliminary analysis suggests that there is no direct correlation between pattern of sympathetic activity and the pattern of arterial pressure changes. Since lability can be markedly attenuated by interrupting neural discharge, and since neural discharge is not well correlated with arterial pressure, we propose that the role of sympathetic discharge in the generation of lability is a permissive one. For example, fluctuations in the contractile activity of vascular smooth muscle might be produced by humoral factors or factors intrinsic to the muscle, but these variations might depend on the presence of sympathetic discharge to the blood vessel wall, at least when sympathetic discharge is present. In the absence of sympathetic influence on the vessels, lability is greatly reduced, but can be enhanced by a wide variety of endogenous vasoconstrictor substances.

Anesthetics are known to blunt the baroreceptor reflex (Stoelting, 1987). All of the inhalation agents affect baroreceptor function to some degree. The depression of the baroreceptor reflex is less with isoflurane than with other agents (Kotrly et al., 1984). Other research has found that

modest amounts of isoflurane may affect baroreceptor activity (Duke, Hill & Troskey, 1982). Seagard et al. (1983) state that isoflurane preserved baroreceptor activity at 1 minimum alveolar concentration (MAC) provided the subject's blood pressure was maintained near normal. When blood pressure is permitted to decrease during isoflurane administration, the tachycardiac response to decreases in pressure were significantly blunted at 1 MAC. If pressures during the administration of the agent are kept within range, then baroreceptor function remains intact until 2 MAC is reached (Seagard et al., 1983).

Anatomy of the larynx. The larynx is a boxlike structure anterior to the bodies of the 4th, 5th and 6th cervical vertebrae (see Figure 5). The larynx consists of four major cartilages two arytenoids, one thyroid, one cricoid; and five accessory cartilages: two corniculate, two cuneiform and the epiglottis (Miller, 1986).

The entire motor and sensory supply to the nine intrinsic muscles of the larynx is derived bilaterally from two branches of the vagus nerve (see Figure 5), the superior laryngeal nerve and the recurrent laryngeal nerve (Miller, 1986). The superior laryngeal nerve divides into external and internal branches. The external branches provide motor innervation of the cricothyroid muscles; the internal branches provide sensory innervation to the epiglottis, base of the tongue, and inferior of the larynx to the vocal

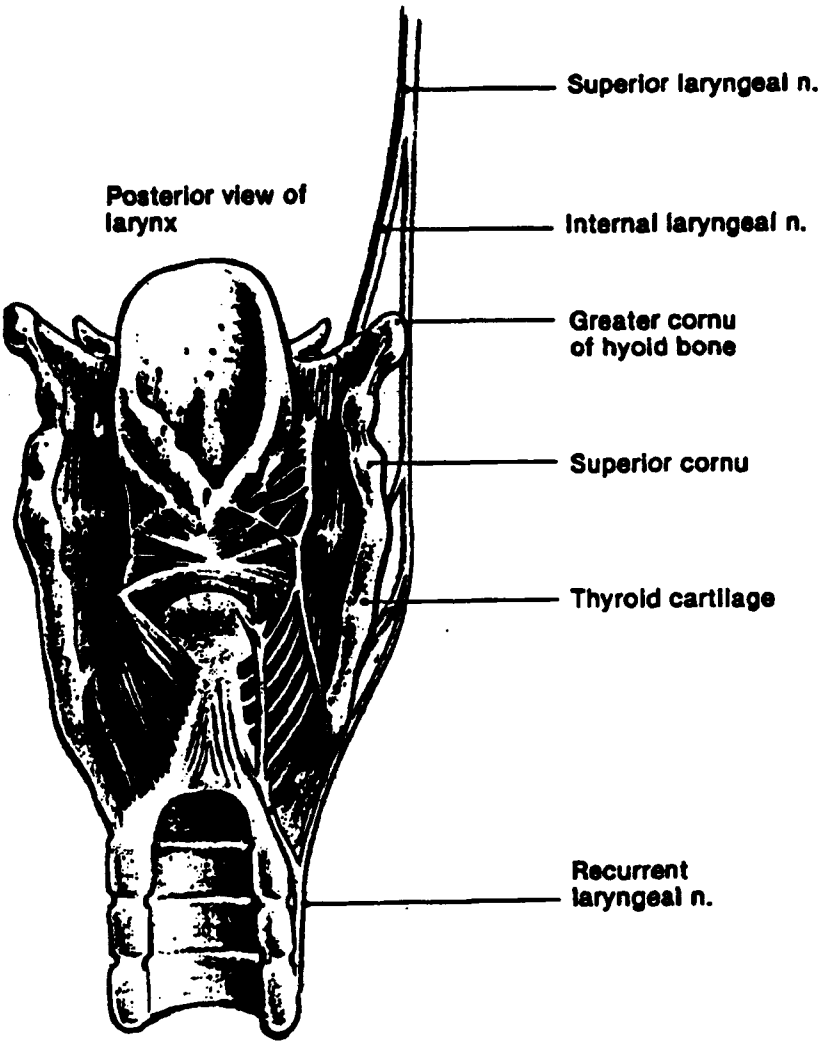


Figure 5. Posterior view of the larynx showing autonomic innervation.

Note. From Atlas of Regional Anesthesia (p. 59) by J. Katz, 1985, Norwalk: Appleton.

cords. The internal branch passes below the greater cornu of the hyoid bone and enters the larynx by piercing the thyrohyoid membrane.

Branches of the superior laryngeal nerve innervate the base of the tongue, epiglottis, and the laryngeal mucosa as far inferiorly as the vocal cords. The recurrent laryngeal nerve provides sensory innervation to the infraglottic larynx and trachea. It also supplies motor innervation to all muscles of the larynx except the cricothyroid muscles.

Stimulation of nerve endings in the pharynx, larynx and trachea activate a reflex response mediated by the vagus nerve, the sympathetic nervous system, and spinal cord. The vagal response consists of bradycardia, hypotension, arrhythmias, apnea, laryngospasm, and bronchospasm. The sympathetic response consists of an increase in sympathoadreanal activity resulting in tachycardia, hypertension, and arrhythmias. The spinal cord reflex consists of coughing, involuntary "bucking" type movements, and vomiting. Due in part to the differences in baseline autonomic tone, vagal responses dominate in children; sympathetic responses dominate in the adult (Appelbaum & Bruce, 1976; Berstein, Nelson, Ebert, Woods & Roerig, 1987; Latto & Rosen, 1985).

Oral endotracheal intubation is most safely performed with direct laryngeal visualization. To insert an oral endotracheal tube under direct laryngeal visualization one

must visualize and elevate the epiglottis. There are two techniques to raise the epiglottis. The straight or the Miller blade is inserted beyond the epiglottis which is raised by the tip of the blade. Under the epiglottis, the glottis comes into view. The curved or Mackintosh blade is inserted into the angle made by the tongue and the epiglottis, known as the Vallecula (Miller, 1986).

By lifting the base of the tongue, the epiglottis is also raised and the glottis comes into view. The anterior aspect of the epiglottis is supplied by the IX th CN (glossopharyngeal). The posterior (Inferior) aspect of the epiglottis is supplied by the superior laryngeal nerve. The superior laryngeal nerve also supplies the base of the tongue and inferior larynx down to the vocal cords. Either approach to intubation stimulates the superior laryngeal nerve (Miller, 1986).

SUMMARY

The induction of anesthesia using intravenous agents became popular in the 1950's. This type of induction replaced inhalation techniques. The intravenous induction offered the benefits of a shorter induction time, and promoting assurance of airway protection. However, the anesthetist had to accept the cardiovascular responses associated with laryngoscopy and oral endotracheal intubation produced during anesthesia.

A endotracheal tube in the larynx is an exceedingly noxious stimulus. The upper airway, larynx, trachea and carina are richly innervated by both the PNS and SNS (Tomori & Widdicombe, 1969). The most obvious example of a motor response is the glottic closure reflex or laryngospasm. The afferent pathways for several reflexes that result in laryngospasm and cardiovascular responses to tracheal intubation are mediated by the glossopharyngeal nerve superior to the anterior surface of the epiglottis, and by the vagus nerve from the level of the posterior epiglottis distally into the lower airway. The laryngeal closure reflex is considered a monosynaptic response that is elicited under light general anesthesia when vagally innervated sensory endings in the upper airway are stimulated (Laurito, Baughhman, Polek, Riegler & Vadeboncourer, 1987; Leicht, Wisborg & Chraemmer-Jorgensen, 1985).

The cardiovascular response to tracheal intubation is mediated by both the SNS and the PNS. The autonomic equivalent of laryngospasm is the sinus bradycardia often induced in infants and small children by endotracheal intubation. This same bradycardia has been demonstrated in some adults as well. Since this reflex is mediated by increased vagal tone at the sinoatrial node, like the laryngospasm, it is considered a monosynaptic response to noxious stimuli. The more common hypertensive and

tachycardiac responses to tracheal intubation are generated by sympathetic efferents. The polysynaptic pathways from the vagal and glossopharyngeal afferents to the sympathetic nervous system via the brainstem and spinal cord assure the diffuse autonomic response which includes excitation of cardioacceleration fibers, release of norepinephrine from adrenergic nerve terminals, and secretion of epinephrine from the adrenal medulla (Robertson, 1978; Russell, Morris, Frewin & Drew, 1981).

Since the cardiovascular responses to laryngoscopy and intubation were first recognized, researchers have been searching for methods to decrease or eliminate it. These methods can be divided into three groups (a) topical anesthesia, (b) intravenous agents and (c) anesthetic depth.

Lidocaine has been postulated to work in part by both the topical anesthesia route and intravenously resulting in a deepening of the level of anesthesia; labetalol controls the cardiovascular response to laryngoscopy by selective alpha and non selective beta blockade.

Chapter Two

Review of Literature

The Cardiovascular Response to Laryngoscopy

There is an abundance of literature that examines the different methods of blunting the hemodynamic response to oral endotracheal intubation. Among the methods used to decrease the circulatory responses are administration of inhalation anesthesia, intravenous opioids, topical or intravenous lidocaine, and intravenous adrenergic blocking agents (Barash et al., 1989). The cardiovascular response to laryngoscopy was first described in 1951 (King et al., 1951). Over the years, many factors which affect the magnitude of the cardiovascular response to intubation have been studied. These studies have led to hypoxia and hypercapnia being eliminated, as they were shown to be relatively unimportant in contributing to this response (King et al., 1951; Hackman, Long and Kruperman, 1955; Stoelting, 1987). Other factors such as length of laryngoscopy, type of laryngoscope blade used and history of hypertension have been found to be involved in the cardiovascular response and ongoing studies continue.

Historically, it was noted by King et al. (1951), in clinical practice, that laryngoscopy and endotracheal intubation resulted in the elevation of heart rate and blood pressure. The noxious stimuli of laryngoscopy and endotracheal intubation, in combination with light anesthesia, resulted in tachycardia and hypertension. King et al. (1951) established that the physiologic response of tachycardia and hypertension may stress the myocardium. These researchers conclude that an individual with compromised cardiovascular status might not be able to tolerate this stress.

Early investigation by King et al. (1951) measured the hemodynamic response to laryngoscopy and oral intubation under light anesthesia. They demonstrated that an elevation of blood pressure occurred within 5 seconds after laryngoscopy. During oral intubation, the average increase in systolic blood pressure reached 53 mm Hg and diastolic blood pressure reached 34 mm Hg. Blood pressure remained elevated for 1 to 2 minutes after the stimulus of laryngoscopy was removed. However, blood pressure gradually returned to base line over 5 minutes (King et al., 1951).

The effect of hypoxia on the cardiovascular response was eliminated by King et al. (1951), who showed pre-oxygenation prevented the tachycardia and hypertension seen in the early stages of hypoxia. This conclusion was supported in later studies that controlled for hypoxia and

found it to be insignificant in effecting the cardiovascular response to endotracheal intubation (Hachman et al., 1955; Stoelting, 1987). The possible effects of hypercapnia on the cardiovascular response to intubation were also eliminated by two studies that showed hypercapnia did not occur to any great extent during the induction of general anesthesia (Stoelting, 1987; Denlinger, Ellison & Ominsky, 1974).

There are several factors that do affect the cardiovascular response to intubation. These include, but may not be limited to, the type of laryngoscope blade used, the length of laryngoscopy and intubation, and history of hypertension (Takeshina, Noda & Higshi, 1964). The effect of the type of laryngoscope blade, straight versus curved, is debatable. King et al. (1951) states that the type of blade used is not a factor in the degree of response observed. Takeshina et al. (1964) suggest that the curved blade has a more pronounced effect on heart rate than the straight blade. This in turn is disputed by several studies which use either the straight or curved blade with similar results (Delinger et al., 1974; Stoelting, 1977). Furthermore, Meikelejohn and Coley (1989) using 23 patients found no difference in cardiovascular response to nasal intubation of the trachea with and without laryngoscopy. They found significant increases in systolic and diastolic pressures after tracheal intubation in both groups. The

values at 1 minute after intubation are significantly higher in the group undergoing laryngoscopy and intubation compared with the group undergoing blind nasal intubation.

Takeshina et al. (1964) found that endotracheal tube cuff inflation had no effect on heart rate or blood pressure. Prys-Roberts, Green, Meloche and Foex (1971) found that hypertension and tachycardia subsided once the laryngoscope blade was withdrawn. They also found the hypertensive patient had a more pronounced rise in pulse rate and blood pressure regardless of whether or not the patient received anti-hypertensive therapy. This finding was particularly true when compared to normotensive patients.

In 1977, Stoelting demonstrated progressively increased mean arterial pressure with the duration of laryngoscopy. The response reached 90% of its maximum value at 45 seconds so that little additional change occurred with prolonged attempts. Fox, Sklar, Hill, Villansculva, and King (1977) cited two case reports of complications resulting from the cardiovascular response to laryngoscopy. In the first case, a 25 year old multigravida presented for emergency cesarean section. During the surgery, she became increasingly hypertensive and tachycardiac. After laryngoscopy and intubation, she developed pulmonary edema and required post operative mechanical ventilation. In the second case, a 37 year old man with end stage renal disease and hypertension

presented for renal transplantation. During laryngoscopy and intubation, hypertension and tachycardia developed with a resultant ventricular arrythmia. These cardiovascular responses were treated with lidocaine and the blood pressure was treated with halothane administration. The patient never regained consciousness and subsequently died. A ruptured cerebral aneurysm was identified on post mortuum autopsy. From these studies originates the currently accepted concept of a sympathetic response to laryngoscopy and intubation leading to hypertension and tachycardia (Fox et al., 1977; King et al., 1951; Prys-Roberts et al., 1971; Stoelting, 1977; Takeshima et al., 1964).

Methods to Attenuate the Cardiovascular Response to Laryngoscopy

When the pressor response to laryngoscopy and endotracheal intubation was recognized, investigators sought methods to decrease or abolish this reflex. Several different techniques were attempted which included increasing the depth of anesthesia by use of inhalation agents, narcotics or topical anesthetics. The use of IV lidocaine has been advocated since the 1940's (Bidwai, Rogers & Stanley, 1979; Black, Kay & Healy, 1984; Rudd & Blaschke, 1985). More recently the use of alpha and beta-adrenergic blockade has been explored to attenuate the sympathetic response and avoidance of surgical stimulation

(Steinhaus & Howland, 1958). Several studies using a variety of these techniques were undertaken.

Anesthetic level. King et al. (1951) documented that increasing the level of inhalation anesthesia decreases the cardiovascular response to laryngoscopy. This method usually involved a deep plane of anesthesia prior to laryngoscopy and intubation. This level of anesthesia decreased the impulses transmitted by the visceral afferent fibers of the larynx, pharynx, and trachea, thereby reducing the cardiovascular response to endotracheal stimulation (Wyke, 1968). In present day practice, inhalation anesthetic agents are easily supplemented with narcotic agents. The advantage of supplementing with narcotics include the ability to produce deep levels of anesthesia without significant cardiovascular depression. Disadvantages include chest wall rigidity, occurrence of bradycardia and hypotension, postoperative respiratory depression, and myocardial depression when combined with other agents.

Tammisto and Aromaa (1977) reported that pentothal and fentanyl could decrease the cardiovascular response to laryngoscopy and intubation. They found that 1 ug/kg of fentanyl in combination with 6 mg/kg of thiopental was as effective as doubling the dose of thiopental. When patients were induced with thiopental 6 mg/kg, fentanyl 2 ug/kg and succinylcholine 1.5 mg/kg, all but 10% of the patients

tolerated the stimulation of an oral endotracheal tube. Bennett and Stanley (1980) found that fentanyl 4 ug/kg combined with 60% nitrous oxide and succinylcholine 1.5 mg/kg was effective in preventing the cardiovascular response to laryngoscopy and intubation. They also reported similar findings with meperidine but not with morphine. Kautto (1982) demonstrated that fentanyl when used with 50% nitrous oxide at a dose of 2 ug/kg significantly attenuated the stress response to laryngoscopy, while nitrous oxide and fentanyl at a dose of 6 ug/kg completely attenuated the response. Although fentanyl has been shown to control the cardiovascular response to intubation, there are several reasons why this was not accepted as routine clinical practice. The doses used by Bennett and Stanley, and Kautto would result in the average person of 60 kg receiving 280 - 420 ug of fentanyl. These doses have been associated with the following undesirable side effects respiratory depression, stiff chest, bradycardia and prolonged emergence from anesthesia.

Lidocaine. Intravenous infusions of local anesthetics are experiencing renewed interest as an adjunct to general anesthesia and a means of alleviating acute and chronic pain. As adjuncts to general anesthesia, infusions of lidocaine have been used to supplement thiopental and inhalation anesthesia (Hines, Difazio & Burrey, 1977; Steinhaus & Howland, 1958). Hines et al. (1977) report that

intraoperative infusions of lidocaine lowered the anesthetic requirements when used with nitrous oxide and halothane. Hines et al. (1977) calculated that lidocaine is capable of contributing a maximum MAC equivalent of 0.4 in rats, and in humans a lidocaine plasma level of 3.2 ug per ml is equated with approximately 1 MAC when administered in conjunction with 70% nitrous oxide.

Using 135 patients, Steinhaus and Howland (1978) used thiopentothal, nitrous oxide, and lidocaine as a supplement to general anesthesia. All patients were induced using pentothal 2 mg per pound (4.4 mg/kg) of body weight, 70% nitrous oxide and 30% oxygen was administered in a semiclosed system. A dose of lidocaine, equivalent to the thiopentothal dose, was administered intravenously over a 5 minute time period. During the surgical procedures, the patients received intermittent injections of thiobarbiturates and lidocaine in equal amounts. There was one reported instance of frank convulsions which was suppressed with an extra 100 mg of thiobarbiturate. Circulatory depression was not "a serious problem"; two patients encountered "severe" hypotension which resolved 10 minutes after lidocaine was discontinued. The chief benefit these authors noted was the marked decrease of pharyngeal and laryngeal reflexes.

In a similar study conducted by Kimmey and Steinhaus (1959), lidocaine and procaine was compared as adjuncts to

general anesthesia. Their goal was to attenuate the cardiovascular response to surgical stimuli. Two groups of males were included in each study group. All groups received thiopentothal 4.4 mg/kg, 70 % nitrous oxide and either 2.2 mg/kg procaine or lidocaine, or 1.1 mg/kg procaine or lidocaine. In the procaine series, 50% of the procaine dosages resulted in an insignificant fall in blood pressure. In contrast to procaine, lidocaine administration was followed by a rise in blood pressure 50% of the time. These rises were slight and considered insignificant. No EKG changes were noted in either group. It was concluded that the lack of vasomotor depression with the administration of lidocaine and its usefulness as an adjunct to general anesthesia was confirmed. This was similar to the results obtained by Blancato, Ping & Alonsable (1969). Lidocaine was shown to be effective in decreasing the amount of narcotic needed for endoscopy.

The mechanism by which systemically administered lidocaine produces analgesia is still the subject of speculation. Hypotheses have been proposed that implicate the peripheral sensory nociceptor, as well as the spinal polysynaptic pathways and supraspinal sites of action in the CNS.

Horrobin and Manku (1977) suggest that lidocaine may inhibit the activity of prostaglandins. These complex fatty acids sensitize peripheral nociceptor to painful stimuli

which results in an overall reduction in pain sensation similar to that seen with nonsteroidal anti-inflammatory medications. As a result of prostaglandin-lidocaine antagonism, it appears that lidocaine much like the nonsteroidal anti-inflammatory medications exhibit similar properties. They both have a limit to the amount of pain they can relieve. Attempts to control pain by increasing the amount of either drug above this level appears to be of no increased value (Horrobin and Manku 1977).

Stoelting (1977) presented evidence that the addition of viscous lidocaine to the epilarynx attenuated the heart rate and blood pressure response to varying lengths of laryngoscopy (ie. 15, 30, and 45 seconds). Patients treated with lidocaine failed to experience significant increases in blood pressure until after 30 seconds. The control group was observed to have a significant pressor response after only 15 seconds.

In 1978, Stoelting confirmed that viscous lidocaine and intravenous lidocaine minimizes pressor responses following intubation, if laryngoscopy lasted longer than 30 seconds. It was concluded that if laryngoscopy was less than 30 seconds duration, viscous and intravenous lidocaine was not useful in attenuation of cardiovascular response to intubation. Denlinger et al. (1974) administered a 4% lidocaine tracheal spray prior to intubation. Results from the study indicated that there was no significant rise in

systolic blood pressure with the lidocaine group. Patients in the control group demonstrated a 30 torr rise in peak systolic blood pressure within 1 minute after intubation.

Hamil, Bedfore, Weva and Colohan (1981) compared the effects of intravenous lidocaine verses laryngotracheal topical lidocaine. They were interested in identifying a preferred route for the administration of lidocaine prior to endotracheal intubation. In addition to measuring heart rate and blood pressure, these authors measured intracranial pressure (ICP) to see if either route was preferable in preventing a rise in ICP. The patients were randomly assigned to each group. Each subject received the same induction protocols, thiopentothal 3 mg/kg and succinylcholine 1.5 mg/kg. One minute after laryngoscopy and endotracheal intubation 50 % nitrous oxide and 50% oxygen was administered. Using a #3 Mackintosh laryngoscope blade, 11 patients received laryngotracheal 4 % lidocaine, via a "laryngotracheal anesthesia" (LTA) set. The other eleven patients received lidocaine 1.5 mg/kg IV. Two minutes after induction, laryngoscopy was performed with a Mackintosh blade. Endotracheal intubation was accomplished in 20 seconds. There was no differences between groups with regards to age, heart rate, base line blood pressure prior to intubation. The group which received laryngotracheal lidocaine showed significant rises in heart rate, blood pressure and ICP which remained elevated for 2 minutes. The

group which received IV lidocaine showed significant rises in heart rate and blood pressure. However this rise was limited to 1 minute, after which cardiovascular values returned to base line. ICP in the group which received IV lidocaine did not significantly increase after endotracheal intubation. This data suggests that IV administration of lidocaine is the preferred technique for administering lidocaine prior to endotracheal intubation.

Abou-madi, Keszler and Yacomb (1977) compared the efficacy of intravenous lidocaine 0.75 mg/kg and 1.5 mg/kg as protection against cardiovascular responses associated with laryngoscopy and endotracheal intubation. These researchers found that 1.5 mg/kg of lidocaine afforded complete protection against cardiac arrhythmias of all types; the lower dose was ineffective in preventing ventricular arrhythmias. The higher dose also offered "borderline" protection against rise in heart rate and blood pressure. The lower dose only prevented a rise in systolic blood pressure.

Labetalol. The efficiency of labetalol in attenuating the rise in heart rate and blood pressure has been well documented (Brittain & Levy, 1976; Hansson & Hannel, 1976; Koch, 1976; Louis, McNeil, & Drummer, 1984; Lund-Johnson, 1984; Martin, Hopkins, & Bland, 1976; Molinoff, 1984; Richards, 1976;). Lavies, May, Achola and Fell (1989) studied labetalol's ability to suppress pressor and

catecholamine responses following laryngoscopy and intubation. The sample consisted of nine patients with pregnancy-induced hypertension and eight with normotensive blood pressures. The experimental group received oral labetalol as antihypertensive therapy. The control group received no placebo. One minute after intubation, mean arterial pressure increased significantly from pre-induction values in both groups. Three minutes after intubation, blood pressure in the control group continued to rise. Hypertension was treated with inhalation agents and blood pressure returned to control levels.

Fischler et al. (1989) studied patients with coronary artery disease to determine the effect of intravenous labetalol on the cardiovascular response to tracheal intubation. Thirty patients were randomly assigned to one of two study groups: a labetalol group and a placebo group. Twelve hours prior to induction, the experimental group received a bolus of labetalol 0.5 mg/kg followed by a constant infusion of 0.1 mg/kg/hr. The placebo group results were consistent with a nonattenuated response to intubation (i.e. tachycardia, hypertension and occasional arrythmia). In the experimental group, labetalol suppressed the hemodynamic response to intubation. These authors also noted a lack of arrythmia or ST segment changes on EKG and felt that labetalol was useful for patients with coronary artery disease who had normal left ventricular function.

Leslie, Kalayjian, McLaughlin and Plachetka (1989) also studied the effect of labetalol on attenuating the hemodynamic response to endotracheal intubation. Sixty patients were randomly assigned to a control, or 1 of the 4 labetalol groups. Labetalol doses of 0.25, 0.5, 0.75 and 1 mg/kg were administered. Five minutes after administration of the study drug, all patients received thiopentathol 4 mg/kg, and succinylcholine 1 mg/kg. General anesthesia using 70 % nitrous oxide and 30% oxygen was maintained for 10 minutes after intubation. These researchers found a dose dependent attenuation of heart rate and blood pressure in those patients treated with labetalol. This attenuation of heart rate and blood pressure was not demonstrated in the control group.

Comparison of Lidocaine and Labetalol

Roelofse, Shipton, De V. Joubert and Groptepass (1987) compared labetalol, acebutolol and lidocaine for controlling the cardiovascular responses to endotracheal intubation. Eighty patients undergoing oral surgery procedures were studied. Each was randomly assigned to either one of the treatment groups or to the control group. Each patient was preoxygenated with 100% oxygen for 2 minutes. One minute prior to induction of anesthesia, group 1 received labetalol 1 mg/kg, and group 2 received acebutolol 0.25 mg/kg, group 3 received lidocaine 2 mg/kg. The control group received

saline 1 ml, 2 minutes prior to induction of anesthesia. There was no significant difference in regards to age, sex or ASA status between the groups. Heart rate, EKG and blood pressure were measured in the same manner. Anesthesia was induced with etomidate 0.3 mg/kg, to a maximum dose of 20 mg. Relaxation was achieved with succinylcholine 1 mg/kg. The patients were then manually ventilated with a mixture of 70% nitrous oxide and 30% oxygen, and then intubated. Four percent enflurane was added and ventilation assisted until spontaneous breathing was resumed, at which point enflurane was decreased to 2%. With the lidocaine group, there was no significant difference from the control group in regards to attenuating a rise in heart rate or blood pressure with one exception. Lidocaine group showed no significant rise in diastolic blood pressure. For the acebutolol group, there was an attenuation of rise in heart rate only. During intubation, labetalol significantly suppressed a rise in heart rate and mean blood pressure. This response lasted for an average of 20 minutes.

This study was timed for maximal labetalol onset at the time of laryngoscopy and intubation. The results demonstrated labetalol's capabilities to suppress the cardiovascular responses to endotracheal intubation. A possible weakness of this study was that lidocaine peaked quickly and was rapidly redistributed. It appeared that lidocaine was administered about 4 minutes too early.

Lidocaine has been shown to suppress cough in 100% of those people studied by Yukioika, Yoshimoto, Hishemura and Fujimori (1985) when given 2.0 mg/kg 1 minute prior to endotracheal intubation.

Inada, Cullen, Nemeskal and Tedick (1987) also compared the effect of labetalol and lidocaine on the hemodynamic response to endotracheal intubation. Forty adult patients were randomly assigned into 1 of 4 groups placebo (saline), lidocaine 100 mg, labetalol 5 mg, or labetalol 10 mg. Medications were administered in a double blind fashion 2 minutes prior to laryngoscopy and intubation. Subjects received thiopentothal 3 to 6 mg/kg and succinylcholine 1.5 mg/kg for induction of anesthesia. Following intubation, patients were ventilated with 100% oxygen for 2 minutes, followed by 50% nitrous oxide and 50% oxygen for 4 minutes. During the study, EKG, heart rate, and blood pressure, via an arterial catheter, were measured continuously.

There was no difference between the placebo, lidocaine and labetalol 5 mg group in regards to attenuation of heart rate. Labetalol 10 mg was effective in suppressing increases in heart rate only. All four groups were unsuccessful in preventing a hypertensive response to endotracheal intubation. Two patients developed minimal wheezing after intubation, one in the placebo group and one in the labetalol 5 mg group. Three patients developed inconsequential arrhythmias which resolved without

treatment. This study, like that of Roelofse et al. (1987), was well conducted but may be improved upon by changing the times the drugs were administered to coincide more closer with the anticipated plasma peak levels. The researchers conclude that, when small doses of labetalol were given, the optimal time the medication is administered should be closer to time of laryngeal stimulation. These researchers felt that this optimal time was between 3 and 5 minutes prior to the stimulation of endotracheal intubation.

Summary

Once the cardiovascular response to laryngoscopy was defined, methods to attenuate this response were investigated. Increasing the level of anesthesia using inhalation agents and topical anesthesia were found partially effective. Narcotics have been found to blunt cardiovascular response to laryngoscopy but not without side effects. The use of intravenous lidocaine was found to be beneficial in attenuating the cardiovascular response to laryngoscopy. Labetalol has been shown to be a useful adjunct in attenuating the cardiovascular response to laryngoscopy and intubation.

Narcotics are effective in blunting the cardiovascular response to intubation; however with surgical procedures of short duration, respiratory depression, chest wall rigidity, bradycardia and prolonged emergence may be experienced.

Lidocaine and labetalol have been shown to be of benefit in reducing the cardiovascular response to intubation without side effects associated with narcotics.

Labetalol 10 mg, given 3 to 5 minutes prior to laryngoscopy, has been shown to be beneficial in attenuation of cardiovascular responses to intubation. Intravenous lidocaine, 1.5 mg/kg, has been shown to attenuate the cardiovascular responses to intubation without the side effects associated with narcotics. Several studies have been reviewed which compare lidocaine and labetalol but not at equipotent doses. In the studies reviewed, these two drugs were administered at similar times, prior to the stimulation of laryngoscopy. This study focused on comparing equipotent doses of lidocaine and labetalol, given at a time which resulted in a peak effect for each drug.

Chapter Three

Methodology

Research Design

The research design was a true experimental design. Three groups were compared to determine if there was a difference in the attenuation to the cardiovascular response when either labetalol, lidocaine or normal saline was administered prior to laryngoscopy and oral endotracheal intubation. Subjects were selected from the daily operating room schedule. After consent was obtained, subjects were randomly assigned to either one of the two study groups or the control group. Blood pressure, heart rate and rhythm were monitored at 1 minute intervals throughout the investigation.

Population, Sample, and Setting

Subjects were randomly assigned and included adults age 19 - 55, with ASA classification I and II. Subjects excluded from the study included those with a history of congestive heart failure, unstable angina, bronchospastic disease or bronchodilator use, atrioventricular block,

severe hepatic dysfunction, or ASA status III, IV, V and E. Subjects who were receiving alpha- or beta- blockers were excluded from this study. Pregnant or breast feeding subjects were also excluded from this study. The sample size included 10 participants in each group for a total of 30 participants.

This investigation was conducted in the main operating rooms of an 1,100 bed mid-Atlantic university based teaching hospital. The study received approval from the institution's Committee on the Conduct of Human Resources.

Instrumentation

Blood pressure. Blood pressure was measured by using the Dinamap™, (Critikon, Inc., Tampa, Florida, 33614) an automatic blood pressure monitor. This monitor is capable of measuring blood pressure at a variety of time intervals. Mean arterial pressure, systolic, diastolic, and heart rate are automatically monitored using the oscillometric technique. This is a stepped deflation sequence which determines the parameters in the following manner. The first determination sequence inflates a cuff pressure at 178 mm Hg for the adult and immediately begins its stepped deflation sequence. If the subject's systolic pressure is greater than the initial start inflation pressure or systolic pressure is absent it stops its deflation sequence, inflates to a higher level and begins the stepped deflation sequence

again. It first determines systole, then mean arterial pressure (MAP) from pulses induced in the cuff at varied pressure levels. The Dinamap™ deflates the cuff one step each time it detects 2 pulsations of a similar amplitude; this insures that artifact is not included in the parameter determinations. The time between deflations depends on the frequency of matched pulsations. If the Dinamap™ is unable to detect a pulsation within 1.6 seconds, it will deflate to the next step. At each step, a microprocessor stores the cuff pressure, the matched pulses, the pulse amplitude and the time between successive pulses. The stepped deflation continues until diastole is determined or until total cuff pressure is less than 7 mm Hg. At this point, the cuff deflates to zero, analyzes the stored data and displays the BP, MAP and HR.

Adaptive internal programs reject most artifact and automatically compensate for a wide range of subject variables. Accuracy of the automatic blood pressure monitor is dependant on the use of a proper size cuff and tubing of correct length. Accuracy of readings is enhanced by placing the cuff and arm at heart level. Accuracy is maintained by routine maintenance and calibration. The Department of Biomedical Engineering at the Medical College of Virginia contracts this duty to an outside agency. This maintenance and calibration is performed every 6 months (R. Hummel, Personal Communication, May 31, 1990). According to

clinical evaluations performed by Critikon, the Dinamap™ is very accurate. When compared to central aortic pressures, the mean differences were as follows: systolic ±2.82 mm Hg, diastolic ±0.88 mm Hg, and heart rate -0.23 (Critikon, Inc., Tampa, Florida, 33614).

Electrocardiogram. There are a variety of name brand Electrocardiogram (EGK) monitors used for the study. All monitors used represent state of the art technology. Like the Dinamap™ the EKG monitors are capable of filtering out artifact through internal programs. The EKG monitors are serviced by an outside biomedical firm which performs a routine service to inspect and calibrate the monitors every six months (R. Hummel, Personal communication May 31, 1990). For the purpose of this study, it is assumed that the monitor has face validity and accurately measures heart rate.

Study Protocol

Each subject was randomly assigned to one of the two treatment groups or the control group. A history was taken prior to the institution of the study to ensure that all subjects met study criteria; the consent form was explained and subject's written approval was obtained. Complete confidentiality was maintained during the study. The protocol was conducted in the following manner (see Table 1):

Table 1

Study Protocol

Time (min)	Events
Zero	Patient in room all routine monitors applied, first of 3 base line readings
One and two	Blood pressure, pulse and cardiac rhythm monitored and recorded at 1 minute interval through out the study subject being preoxygenated dTc 3 mg IV administered
Three	Labetalol 10 mg or placebo (NS) IV administered over 2 minutes
five	Thiopental 3 - 5 mg\kg IV administered
Six	Airway assured Sch 1.5 mg\kg IV administered Lidocaine 1.5 mg\kg or Normal Saline administered IV
Seven	Endotracheal Intubation After correct tube placement assured nitrous oxide 50% and oxygen 50% administered
Eight and on to fifteen	Thiopental 25 - 50 mg IV bolus administered as necessary to maintain unconsciousness
Study complete	Add inhalation agent, other agents as necessary

1. An intravenous catheter was inserted in an upper extremity for infusion of an IV solution.

2. Subjects received midazolam 2 mg intravenously, in the holding area approximately 15 minutes prior to induction.

3. Upon arrival at the operating suite subjects were identified and assisted onto the operating room table. The following physiologic monitors were applied to each subject (a) electrocardiogram, (b) an automatic blood pressure measuring device, (c) pulse oximeter, and (d) precordial stethoscope. Base line hemodynamic readings were recorded for three consecutive minutes while the subject was preoxygenated with 100% oxygen via a face mask and a semi-closed circle anesthesia system. At time one, all subjects received dTc 3 mg IV to prevent fasciculation from Sch. Blood pressure, pulse and rhythm were continually measured each minute throughout the 15 minute study.

4. Experimental subjects received either labetalol 10 mg or placebo (10 ml. normal saline) slow IV push over 2 minutes.

5. Pentothal 3-5 mg/kg was administered IV to induce anesthesia. Once lid reflex was abolished, and airway assured, succinylcholine 1.5 mg/kg was administered.

6. Immediately following succinylcholine, lidocaine 1.5 mg/kg or placebo (10 ml. normal saline) was administered IV

bolus. All study medications were administered in equal volumes.

7. Endotracheal intubation was performed 60 seconds after lidocaine or placebo was given. Intubation was accomplished in 30 seconds or less.

8. Subjects received a mixture of nitrous oxide 50% and oxygen 50%, and thiopental 25 - 50 mg bolus as necessary to maintain unconsciousness until the conclusion of the 15 minute study. At that time, anesthesia of choice was initiated.

Because of the difference in the onset time between lidocaine and labetalol, the study consisted of three subgroups. Group one received a placebo injection of saline 5 minutes prior to intubation and a second IV injection 90 seconds prior to intubation. Group two received labetalol 10 mg IV bolus 5 minutes prior to intubation and a saline injection 90 seconds prior to intubation. Group three received Saline injection IV bolus 5 minutes prior to intubation and Lidocaine 1.5 mg/kg 90 seconds prior to intubation. Laryngoscopy was performed 60 seconds after the last medication. All drugs were administered in equal volumes. All medication needed for the study were on formulary and were routinely administered in the operating room.

Statistical Analysis

The variables were analyzed by repeated measures of covariance (ANCOVA), with the baseline measure as the covariate. The covariate was an average of the first three readings of heart rate and blood pressure prior to the administration of lidocaine, labetalol, or placebo. ANCOVA tests the significance of differences between group means after first adjusting the scores on the dependent variables to eliminate the effects of the covatiate. A p value of less than .05 was considered significant.

Chapter Four

Results

The purpose of the study was to determine what effect lidocaine 1.5 mg/kg, or labetalol 10 mg given intravenously would have on the cardiovascular response to laryngoscopy and oral endotracheal intubation when compared to a placebo. The sample consisted of 30 adult patients who were randomly assigned to one of two treatment groups or control group. There were no significant differences between the three groups with respect to ASA classification, age, gender and weight (see Table 2). All 30 subjects followed the same induction procedures with the exception of the study medications used. The variables recorded were (a) heart rate, (b) systolic blood pressure, (c) diastolic blood pressure and (d) cardiac rhythm.

The independent variables were lidocaine 1.5 mg/kg and labetalol 10 mg. Age, weight and gender were controlled for by randomization. Laryngoscopy was limited to 30 seconds. The dependent variables, heart rate, blood pressure and cardiac rhythm were recorded every minute for the duration of the study. Observation and recording cardiovascular data occurred every minute. The first three observations were

Table 2

Group Characteristics

Characteristic	Group		
	Control (n = 10)	Labetalol (n = 10)	lidocaine (n = 10)
ASA I	5	3	6
ASA II	5	7	4
Male	4	5	4
Female	6	5	6
Age (years)	38	32.2	32
weight (kg)	77.5	79.4	77.3

Note: Values were reported as mean, except for ASA classification and gender, which were reported as number of patients.

averaged to obtain the "baseline," followed by another 13 observations at 1-minute intervals. The variables were analyzed by a repeated measures analysis of covariance with the baseline measure as the covariate. The results are summarized below.

Table 3

Heart Rate

ANCOVA SUMMARY for HR

Source	Sum of sqs.	df	Mean Sq.	F-ratio	p
Between					
Group	1,185.527	2	592.763	.800	.460
Error	19,260.506	26	740.789		
Within					
HR	12,985.135	11	1,180.467	14.047	< .001
HR x Group	3,047.905	22	138.541	1.649	.036
Error	24,033.870	286	84.035		

Between Group Effect

The Between group effect is not significant ($p = .460$). This indicates that each group mean calculated from the 13 changes from each subjects baseline, respective of their group, does not differ from the grand overall mean; therefore, the groups do not differ from each other.

Within Group Effect

The Within HR effect is significant ($p < .001$). This indicates that the 13 means across all 3 groups differ from the grand mean and from each other. Heart rate varies over time. This effect can be seen on Figure 6 which shows significant change in heart rate from base line measurements. The effect of the interaction between HR and Group is significant ($p = .036$). This indicates that the

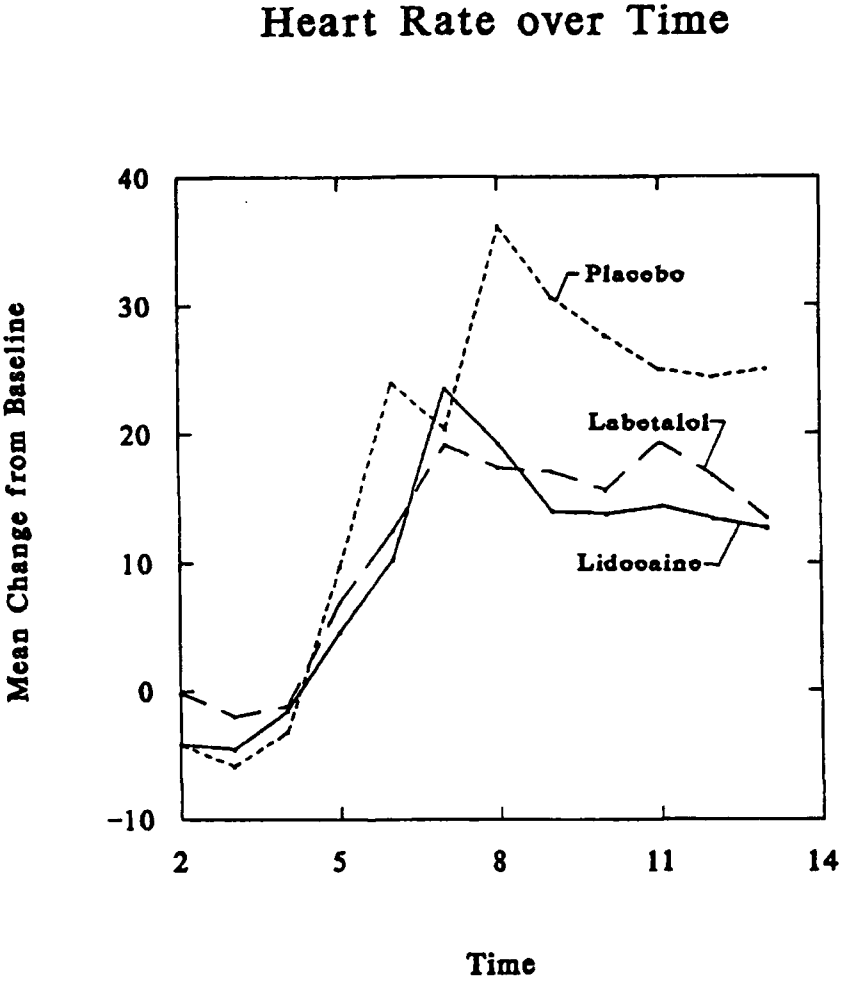


Figure 6. Heart rate response by group.

Note: Mean changes from baseline are recorded as mm Hg, time is recorded in minutes.

pattern of HR change over time is different in the three groups. This also can be seen in Figure 6 which plots the mean changes from baseline by group. The interaction effect between group and heart rate is best described by the lack

of parallelism. The lack of parallelism is illustrated in Figure 6.

Table 4

Systolic Blood Pressure

ANCOVA Summary for SBP

Source	Sum of Sqs.	df	Mean Sq.	F-ratio	p
Between					
Group	5,007.857	2	2503.925	2.103	.142
Error	30,959.182	26	1190.738		
Within					
SBP	3,591.114	11	326.465	1.983	.030
SBP x Group	5,927.564	22	269.435	1.636	.038
Error	47,095.822	286	164.671		

Between Group Effect

The Between Group effect is not significant, although it approaches significance ($p = .142$). This means that each group mean, calculated from the 13 changes in systolic blood pressure (SBP) for all 10 subjects differs only slightly from each other.

Within Group Effect

The within SBP effect is significant ($p = .030$). This indicates that the 13 means across all 3 groups differ from the grand mean and from each other. SBP within each group varies over time. This can be seen in Figure 7 which

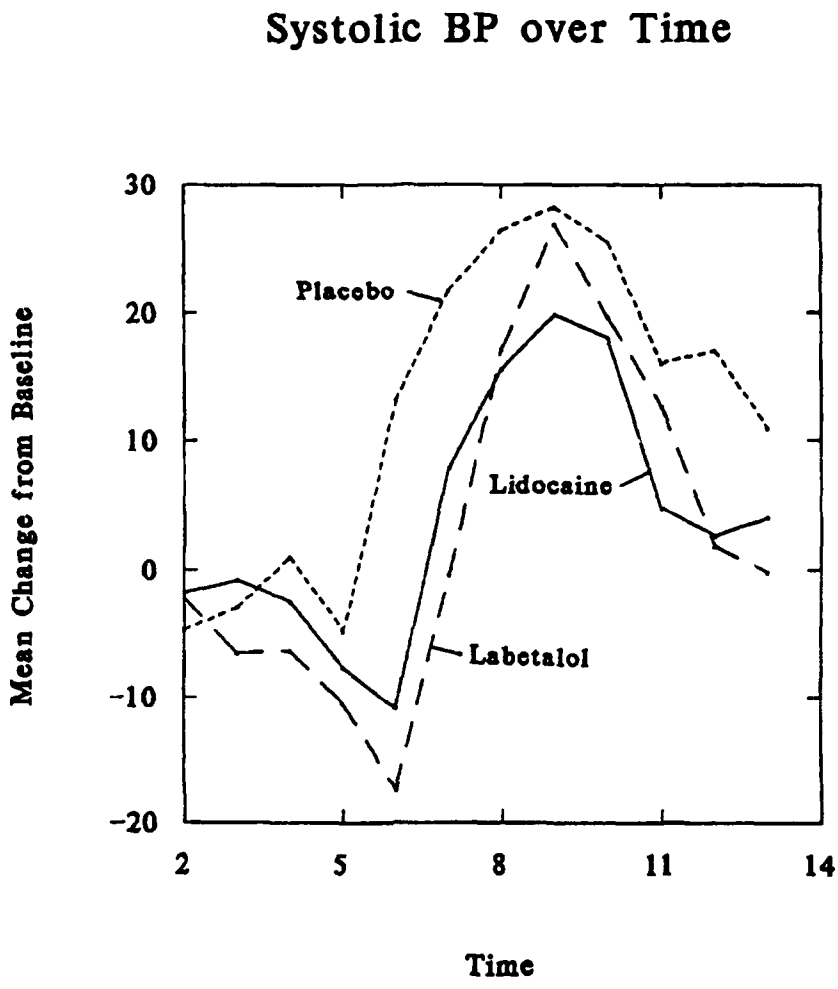


Figure 7. Systolic blood pressure by group.

Note: Mean changes from baseline are recorded as mm Hg, time is recorded in minutes.

suggests significant changes in blood pressure from baseline. The effect of the interaction between SBP and group is significant ($p = .038$). This indicates that the pattern of SBP change over time is different in the three groups. This plots the mean changes from baseline by group.

The interaction effect is best illustrated by the lack of parallelism between groups. This interesting effect is illustrated in Figure 7.

Table 5

Diastolic Blood Pressure

ANCOVA Summary for DBP

Source	Sum of Sqs.	df	Mean Sq.	F-ratio	p
Between					
Group	326.656	2	163.328	.261	.772
Error	16,528.985	26	625.346		
Within					
DBP	621.651	11	56.514	.477	.917
DBP x Group	2,869.357	22	130.425	1.100	.345
Error	33,899.016	286	118.528		

Between Group Effect

The between group effect is not significant ($p = .772$). This indicates that each group mean, calculated from the 13 changes in diastolic blood pressure (DBP) for all 10 subjects does not differ from each other.

Within Group Effect

The within DBP effect also is not significant ($p = .917$). This indicates that the 13 means across all 3 groups differ from the grand mean and from each other. DBP within each group varies over time. This can be seen in Figure 8

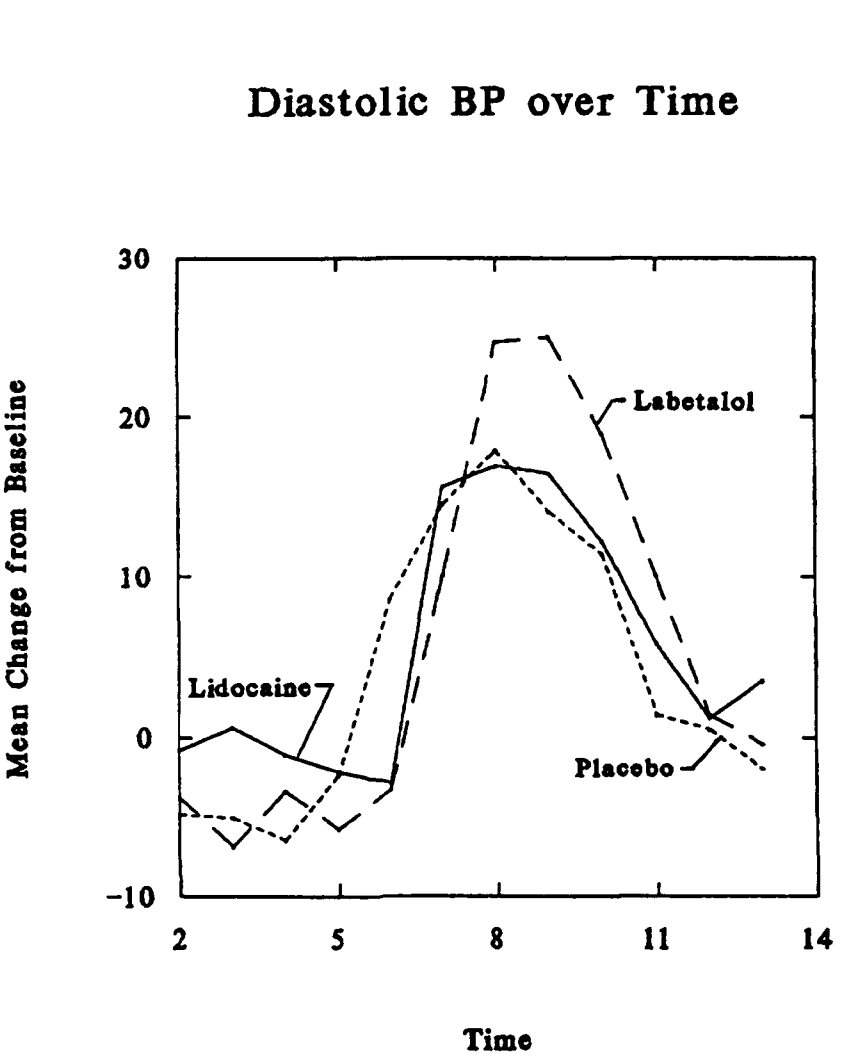


Figure 8. Diastolic blood pressure by group.

Note: Mean changes from baseline are recorded as mm Hg, time is recorded in minutes.

which plots the mean changes from baseline by group. The effect of the interaction between DBP and group is not significant ($p = .345$). This indicates the pattern of DBP over time is not different in the 3 groups (see Figure 8). There is no clear relationship between effect and group.

Chapter Five

Discussion

The purpose of this true experimental study was to determine if there was a difference in the cardiovascular response to direct laryngeal visualization and oral endotracheal intubation in patients receiving either lidocaine 1.5 mg/kg or labetalol 10 mg intravenously. Results obtained from this study indicated there was no statistically significant difference in the attenuation of the cardiovascular response between treatment and control groups. Therefore, the hypothesis failed to be rejected.

Correlation With Previous Studies

Patients receiving labetalol 10 mg and lidocaine 1.5 mg/kg reacted similarly throughout the study. Lidocaine and labetalol were effective in blunting a significant rise in heart rate ($p < .001$) and systolic blood pressure ($p = .030$). This differs from the earlier findings of Inada et al. (1987) who reported that labetalol 10 mg was more effective than lidocaine 1 mg/kg, in attenuating tachycardia in response to laryngoscopy. Roelofse et al.

(1987) also reported that labetalol was more effective than lidocaine in attenuating the rise in heart rate after intubation. The differences in these findings might be explained by examining the dose of medication used and time of administration. Both Roelofse et al. (1987) and Inada et al. (1987) administered lidocaine 2 minutes prior to laryngoscopy and intubation which might account for the differences seen. Inada et al. (1987) used a smaller dose of lidocaine 1 mg/kg; Roelofse et al. used a larger dose 2 mg/kg. It appears that timing may be an important factor in determining the cardiovascular benefit of lidocaine.

Roelofse et al. (1987) found that labetalol 1 mg/kg given as an IV bolus 1 minute before laryngoscopy was not effective in attenuation of heart rate ($p > .01$), systolic ($p > .01$) and diastolic ($p > .05$). Inada et al. (1987) found that 10 mg labetalol was not effective in attenuation of systolic or diastolic blood pressure after laryngoscopy when given 2 minutes prior to endotracheal intubation. During the current study, it was found that labetalol 10 mg given 5 minutes prior to laryngoscopy and lidocaine 1.5 mg/kg when given 60 seconds prior to laryngoscopy had similar results ($p = .30$) in the attenuation of the cardiovascular response to laryngoscopy. As with the heart rate, the difference seen between the studies can be related to the dose of labetalol used or its time of administration in relationship to laryngoscopy. Inada et al. (1987) found

that labetalol 10 mg when given in an IV bolus dose was most effective when given 3 to 5 minutes before tracheal stimulation. When larger doses of labetalol (0.75 mg/kg) was administered 8 to 10 minutes before laryngoscopy, labetalol did not attenuate the cardiovascular response to laryngoscopy (Roselofe et al., 1987). Labetalol 1 mg/kg did block the cardiovascular responses to intubation when given 8 to 10 minutes before laryngoscopy but with risk of hypotension (Leslie et al., 1987).

In this current study, both lidocaine and labetalol were timed to exert their peak effect at the time of laryngoscopy. This was conducted in a double blind manner with labetalol given 5 minutes prior to laryngeal stimulation, and lidocaine administered 60 seconds prior to laryngeal stimulation.

Difficulties With the Study

Due to the nature of this study only healthy (ASA I & II) patients were used. This narrowed the target population considerably. Several anesthesia practitioners voiced concern in participating in a double blind study if labetalol was used due to the reported cases of bronchospasm. One subject in the control group developed hypertension and tachycardia to the extent that treatment was needed. The subject was treated with isoflurane and the heart rate and blood pressure returned to control levels.

Recommendation for Further Study

The following recommendations are made to guide further research in this area.

1. This study should be duplicated with a narcotic preoperative medication to determine if a narcotic preoperative medication when used with either labetalol or lidocaine would better blunt the cardiovascular response to laryngoscopy.

2. This study should be duplicated using labetalol or lidocaine and an appropriate dose of a rapid acting opioid which would allow for effective blunting of the cardiovascular response to laryngoscopy.

Summary

Even though, the hypothesis was not rejected, labetalol 10 mg IV given 5 minutes before laryngoscopy and lidocaine 1.5 mg/kg given 60 seconds before laryngoscopy blunted the rise in heart rate and systolic blood pressure to laryngoscopy. Neither medication was able to prevent a rise in diastolic blood pressure.

References

References

Abou-Madi, M. N., Keszler, H. & Yacoub, M. (1977). Cardiovascular reactions to laryngoscopy and tracheal intubation following small and large intravenous doses of lidocaine. Canadian Anesthetist Society Journal, 24, 12-19.

Ahlquist, R. P. (1948). A study of adrenotropic receptors. American Journal of Physiology. 153, 586-600.

Appelbaum, E. & Bruce, D. (1976). Tracheal intubation, Philadelphia: Saunders, (pp. 15-18).

Barash, P. G., Cullen, B. F. & Stoelting, R. K. (1989). Clinical Anesthesia. (pp. 555-556). Philidelphia: Lippencott.

Bennett, G. M. & Stanley, T. H. (1980). Human cardiovascular responses to endotracheal intubation during morphine - N2O and fentayl - N2O anesthesia. Anesthesiology, 52, 520-522.

Berne, R. M. & Levy, M. N., (1988). Physiology. (pp. 517-520). St Louis: Mosby.

Bernstein, J. S., Nelson, M. A., Ebert, T. J., Woods, M. P. & Roerig, D. C. (1987). Beat by beat Cardiovascular responses to rapid sequence inductions in humans: Effects of Labetalol. Anesthesiology. 67, A32

Bidwai, A. V., Rogers, C. R. & Stanley, T. (1979). Blood-pressure and pulse-rate responses to endotracheal extubation with and without prior injection of lidocaine. Anesthesiology, 51, 171-173.

Black, T. E., Kay, B. & Healy, T. E. J. (1984). Reducing the haemodynamic responses to laryngoscopy and intubation. Anesthesia, 39, 883-887.

Blancato, L.S., Ping, A.T.C. & Alonsable, D. (1969). Intravenous lidocaine as an adjunct to general anesthesia for endoscopy. Anesthesia and Analgesia, 48, 224-227.

Brittain, R. T. & Levy, G. P. (1976). A review of the animal pharmacology of labetalol, a combined alpha-and beta-adrenoceptor - blocking drug. British Journal of Clinical Pharmacology, (Supplement), 681-694.

Dale, H. H. (1906). On some physiological actions of ergot. Journal of Physiology, 34, 163-206.

Denlinger, J. K., Ellison N. & Ominsky, A. J. (1974). effects of intratracheal lidocaine on circulatory responses to tracheal intubation. Anesthesiology, 41, 409-412.

Derbyshire, D. R., Chmielewski, A., Fell, D., Vater, M., Achola, K. & Smith, G. (1983). Plasma catecholamine responses to tracheal intubation. British Journal of Anaesthesia, 55, 855-859.

Dingle, H. R. (1966). Antihypertensive drugs and anesthesia. Anesthesia, 21, 151.

Duke, P. C., Hill, K. & Troskey, S. (1982). Effect of isoflurane with nitrous oxide anesthesia on baroreceptor reflex control of heart rate in many. Anesthesiology, 57, A41.

Exton, J. H. (1985). Mechanisms involved in alpha adrenergic phenomenon. America Journal of Physiology, 248, E3633.

Fischler, M., Dubois, C., Brodaty, D., Schulumberger, S., Melchior, J. C., Guilmet, D. & Vourc'H, G. (1985). Circulatory responses to thiopentone and tracheal intubation in patients with coronary artery disease. British Journal of Anaesthesia, 57, 493-496.

Forbes, M. A. & Dally, F. G. (1970). Acute hypertension during induction of anesthesia and endotracheal intubation in normotensive man. British Journal of Anaesthesia, 42. 618-624.

Fox, J. E., Sklar, G. S., Hill, C. H., Villanueva, R. & King, B. D. (1977). Complications related to the pressor response to endotracheal intubation. Anesthesiology, 47, 524-525.

Fuder H. (1985). Selected Aspects of presynaptic modulation of norepinephrine release from the heart. Journal of Cardiovascular Pharmacology, 7 Supplement 5, s2

Guyton, A. (1986). Textbook of medical physiology. (6th ed). Philadelphia: Saunders, (pp. 165, 246-247, 716-718).

Hackman, R. J., Long, J. H. & Krumperman, L. W. (1955). The changes in blood gases associated with various methods of induction for endotracheal anesthesia. Anesthesiology, 16, 29-40.

Hamill, J. F., Bedford, R. F., Weaver, D. C. & Colohan, A. R. (1981). Lidocaine before endotracheal intubation: intravenous or laryngotracheal? Anesthesiology, 55, 578-581.

Hansson, L. & Hamel, B. (1976). Labetalol, a new alpha - and beta-adrenoceptor blocking agent in hypertension. British Journal of Clinical Pharmacology, (Supplement), 763-764.

Hines, R. S., DifFazio, C. A. & Burney, R. G. (1977). Effects of lidocaine on the anesthetic requirements for nitrous oxide and halothane. Anesthesiology, 47, 437-440.

Horrobin, D.F. & Manku, M.S. (1977) Role of prostaglandins suggested by the prostaglandin agonist/antagonist actions of local anasthetic, anti-arrythmic, anti-malarial, tricyclic anti-depressant and methy xanthine compounds, effects on membranes, and on nucleic acid function. Medicinal Hypotheses, 3, 71-86.

Inada, E., Cullen, D. J., Nemeskal, A. R. & Teplick, R. (1989). Effect of labetalol or lidocaine on the hemodynamic response to intubation: A controlled randomized double-blind study. Journal of Clinical Anesthesia, 1, 207-213.

Jacob, H. J., Barres, C. P., Machaclo, B. H. & Brody, M. J. (1988). Studies on neural and humoral contributions to arterial pressure lability. The American Journal of Medical Sciences, 295(4): 341-348.

Kautto, U. (1982). Attenuation of the circulatory response to laryngoscopy and intubation by fentanyl. Acta Anaesthesiologica Scandinavica, 26. 217-221.

Kimmey, J. R. & Steinhaus, J. E. (1959). Cardiovascular effects of procaine and lidocaine during general anaesthesia, Acta Anaesthesia Scandinavia, 3, 9-15.

King, B. P., Harris, L. C., Greifenstein, F. E., Edder J. D. & Dripps, R. D. (1951). Reflex circulatory responses to direct laryngoscopy and tracheal intubation performed during general anesthesia. Anesthesiology, 12, 556-566.

Koch, G. (1976). Hemodynamic effects of combined alpha-and beta-adenoceptor blocking after intravenous labetalol in hypertensive patients at rest and during exercise. British Journal of Clinical Pharmacology, (Supplement), 725-728.

Kotrly, K. S., Ebert, T. J., Vucins, E., Igler, F. O., Barney, J. A. & Kampine, J. P. (1984). Baroreceptor reflex control of heart rate during isoflurane. Anesthesiology, 60, 173.

Langer, S. Z. (1973). Recent developments in noradrenergic neurotransmission and in relevance to the mechanisms of action of certain antihypertensive agents. Hypertension, 2, 272-382.

Latto, I. & Rosen, M. (1985). Difficulties in tracheal intubation, Philadelphia: Saunders, (pp. 4-7).

Laurito, C. E., Baughman, V. L., Polek, W. V., Riegler, F. X. & Vadeboncourer, T. R. (1987). Aerosolized and intravenous lidocaine are no more effective than placebo for the control of hemodynamic responses to intubation. Anesthesiology. 67, A29.

Lavies, N. G., Meiklejohn, B. H., May, A. E., Achola, A. J. & Fell, D. (1989) Hypertension and catecholamine responses to tracheal intubation in patients with pregnancy-induced hypertension. British Journal of Anesthesia, 63, 429-434.

Leicht, P., Wisborg, T. & Chraemmer-Jorgensen, B. (1985). Does intravenous lidocaine prevent laryngospasm after extubation in children. Anesthesia and analgesia, 64, 1193-1196.

Leslie, J. B., Kalayjian, R. W., McLoughlin, R. M. & Plachetka, J. R. (1989). Attenuation of the hemodynamic responses to endotracheal intubation with preinduction intravenous labetalol. Journal of Clinical Anesthesia, 1, 194-173.

Louis, W. J., McNeil, J. J. & Drummer, O. H. (1984). Pharmacology of combined alpha- and beta-blockade I. Drugs, 28, (supplement 2), 16-34.

Lund-Johnson, P. (1984). Pharmacology of combined alpha- and beta-blockade II: Haemodynamic effects of Labetalol. Drugs, 28, (supplement 2), 35-50.

Martin, L. E., Hopkins, R. & Bland, R. (1976). Metabolism of labetalol by animals and man. British Journal of Clinical Pharmacology, (Supplement), 695-710.

Meikleyon, B. H. & Coley, S. (1989). Pressor and catecholamine response to nasal intubation of the trachea. British Journal of Anaesthesia, 63, 283-286.

Miller, R. D. (ed.). (1986). Anesthesia. (2nd ed.)(Vol 1-3). New York: Churchill Livingstone.

Molinoff, P. B. (1984), Alpha- and beta-adrenergic receptor subtypes: Properties, distribution and regulation. Drugs, 28, (supplement 2), 1-15.

Osswald, W. & Guimaraes S. (1983). Adrenergic mechanism in blood vessels: Morphological and pharmacological aspects. Review of physiology and Biochemical Pharmacology, 96, 53-122.

Prys-Roberts, C., Green, L. T., Meloche, R. & Foex, P. (1971). Studies of anesthesia in relation to hypertension II: Haemodynamic consequences of induction and endotracheal intubation. British Journal of Anaesthesia, 43, 531-546.

Richards, D. A. (1976). Pharmacological effects of labetalol in man. British Journal of Clinical Pharmacology, (Supplement), 721-723.

Robertson, D., (1978). Comparative assessment of stimuli that releases neuronal and adrenomedullary catecholamines in man. Circulation, 59, 637-642.

Roelofse, J. A., Shipton, E. A., De V. Joubert, J. J. & Grotepass, F. W. (1987). A comparison of labetalol, acebutolol, and lidocaine for controlling the cardiovascular responses to endotracheal intubation for oral surgical procedures. Oral Maxillofacial Surgery, 45, 835-840.

Rudd, P. & Blaschke, T. A. (1985). Antihypertensive agents and the drug therapy of hypertension: The pharmacological basis of therapeutics. Goodman, L.S., Gilman, A.G., et al. (ed.), New York: Macmillan. (pp. 720-792)

Russell, R. G., Morris, D. B., Frewin, D.B. & Drew, S.E. (1981). Changes in plasma catecholamine concentrations during endotracheal intubation. British Journal of Anaesthesia, 58, 837-839.

Seagard, J. L., Elegbe, E. O., Hopp, F. A., Bosnjak Z. J., Von Colditz, J. H., Kalbfleisch, J. H. & Kampine, J. P. (1983). Effects of isoflurane on the baroreptor reflex. Anesthesiology, 59, 511-520.

Steinhaus, J.E. & Howland, D.E. (1958). Intravenously administered lidocaine as a supplement to nitrous oxide-Thiobarbiturate anesthesia. Anesthesia and Analgesia, 37, 40-46.

Stoelting, R.K. (1977). Circulatory changes during direct laryngoscopy and tracheal intubation: Influence of duration of laryngoscopy with or without prior lidocaine. Anesthesiology, 47, 381-384.

Stoelting, R.K. (1978). Blood pressure and heart rate changes during short-duration laryngoscopy for tracheal intubation: influence of viscous or intravenous lidocaine. Anesthesia and Analgesia, 57, 197-199.

Stoelting, R.K. (1987). Inhaled Anesthetics. Pharmacology and Physiology in Anesthetic Practice, Philadelphia: Lippincott, (pp. 41-44).

Takeshima, K., Noda, K. & Higaki, M. (1964). Cardiovascular responses to rapid anesthesia induction and endotracheal intubation. Anesthesia and Analgesia, 43, 201-208.

Tammisto, T. & Aromaa, U. (1977). The role of different components of balanced anesthesia in tolerance to endotracheal intubation. Annales Chirurgiae et Gynaecologiae, 66, 247-254.

Tomori, Z. & Widdicombe, J.G. (1969). Muscular, bronchomotor and cardiovascular reflexes elicited by mechanical stimulation of the respiratory tract. Journal of Physiology, 200, 25-49.

West, J.B. (1985). Best and Taylor's Physiological basis of Medical Practice, Baltimore: Williams and Wilkins, (pp. 270-274).

Wycoff, C.C. (1960). Endotracheal intubation: Effects on blood pressure and pulse rate. Anesthesiology, 21, 153-158.

Wyke, B. D., (1968). Effects of anesthesia upon intrinsic laryngeal reflexes. Journal of Laryngoscopy, 82, 603-612.

Yukiola, H., Yoshimoto, N., Nishemura, K. & Fjuimori, M. (1985). Intravenous lidocaine as a suppressant of coughing during tracheal intubation. Anesthesia and Analgesia, 64, 1189-1192.

Appendix

Appendix A

Consent Form

Lauraine Stewart, MD
Department of Anesthesiology
786-1324

Randy L. McGee, RRNA II
Department of Nurse Anesthesia
MCV Office phone 6-9808
Home phone (804) 741-6142

1. Title of Research
   Effect of lidocaine and labetalol on the hemodynamic response to oral endotracheal intubation.

2. Introduction
   I am investigating the effect that preinduction doses of intravenous labetalol and lidocaine will have on Blunting the hearts responses to the placement of an oral breathing tube. You have been selected as a candidate to participate in this study because placement of an oral breathing tube is indicated for your surgical procedure.

3. Benefits
   Hypertension, tachycardia and arrhythmias are common occurrences during the placement of an oral breathing tube. Both lidocaine and labetalol have been shown to partially blunt your hearts responses to the placement of this oral breathing tube. Your participation in this study will help document the degree of blunting that each drug will cause. This information may then be used to predict an optimum dose of drug need to suppress the hearts response to the placement of an oral breathing tube.

4. Alternate Therapy
   I understand that I have the right to choose not to participate in this study. Your refusal of consent to participate will not alter your anesthesia or quality of care.

Pt. int____

5. Risks, Inconveniences, Discomforts

I understand that the risks involved with this study are associated with the side effects of Lidocaine and labetalol. I also understand the risk of receiving a placebo may mean that my hearts responses to placement of an oral breathing tube may not be adequately blunted. The side effects associated with lidocaine include: allergic reaction, central nerves system depression, hypotension, bradycardia, and seizure.
The side effects associated with labetalol include: allergic reaction, hypotension, bradycardia, and bronchospasm.

Assessment of blood pressure, heart rate and electrocardiogram (EKG) is routinely monitored during induction of anesthesia, intraoperatively and postoperatively. For this study we will monitor these parameters every one minute for the first five minutes prior to endotracheal tube placement and for five minutes after endotracheal tube placement. There will be no additional inconvenience to you as a result of this study.

6. Cost of Participation

No additional cost for participation in this study will be accrued. All anesthesia, hospital, and physician's fees will be billed to me in a normal fashion.

7. Pregnancy

If you are pregnant or breast feeding you will not be a candidate for this study. Both lidocaine and labetalol cross the placenta and have been found in breast milk. Since this may have adverse effects on your baby you will not be included in this study.

8. Research Related Injury

I understand that in the event of physical and/or mental injury resulting in my participation in this research project, Virginia Commonwealth University will not offer compensation. If any injury occurs, medical treatment will be available at MCV Hospitals. Fees for such treatment will be billed to me or appropriate third party insurance. If any new information becomes

available to the investigator that may affect my participation in this study, I will be notified.

9. Confidentiality of records

I understand that my physicians and nurses will treat my identity with professional standards of confidentiality. I understand that the information obtained in this study may be published, but that my identity will not be revealed.

10. Withdrawal

If you have any questions regarding the study you are encouraged to ask them now or at any time prior to conduction of anesthesia. In addition, you or your physician may withdraw you from the study at any time.

Signed_____ Witness_____

Date_____ Date_____

Appendix B

DATA COLLECTION FORM

Patient Case #:_____ Date:_____

Weight:_____Kg Age:_____

ASA: 1 2 3 4 5 E Consent:_____

Premedication:_____

Begining Time:_____ Study drug:_____

Time#	Blood Pressure		Pulse	Rhythm
1	_____		_____	_____
2	_____		_____	_____
3	_____	Labet/Placeb	_____	_____
4	_____	push * 2min	_____	_____
5	_____	Pentothal	_____	_____
6	_____	Sux/Lid/Plac	_____	_____
7	_____	Intubate	_____	_____
8	_____	N_2O/O_2	_____	_____
9	_____		_____	_____
10	_____		_____	_____
11	_____		_____	_____
12	_____		_____	_____
13	_____		_____	_____
14	_____		_____	_____
15	_____		_____	_____

Length of laryngoscopy:_____ Blade of Choice:_____

Tube Size:_____ cc of air in cuff:_____

EKG Moniter:_____ Blood Pressure Monitor:_____

Scheduled procedure:

VITA

Randy LeRoy McGee was born December 2, 1954, in Bozeman, Montana, and is an American citizen. He graduated from Kearns High School, Kearns, Utah, in 1973. He received his Bachelor of Arts in Psychology from the University of Utah, Salt Lake City, Utah, in 1979. He served as community based coordinator for United Cerebral Palsy of Utah for 2 years. He received his Bachelor of Science in Nursing from the University of Utah, Salt Lake City, Utah in 1983. In August, 1988, while a 1st Lieutenant on active duty in the United States Air Force, he was sponsored by the Air Force Institute of Technology to attend the Department of Nurse Anesthesia, School of Allied Health Professions, Virginia Commonwealth University.